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Fast and Efficient Method for Quantitative Reduction of Carbonyl Compounds by NaBH₄ under Solvent-Free Conditions

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Abstract

Reduction of different aldehydes and ketones were efficiently accomplished by sodium borohydride in a ball-mill under solvent-free conditions.

Introduction

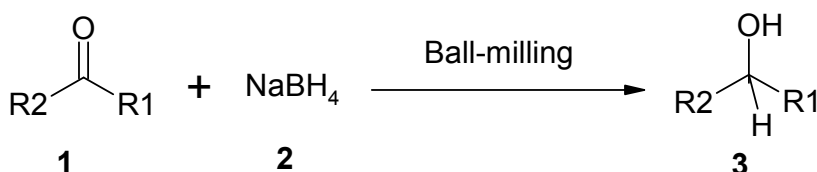
Reduction is one of the frequently used reactions in organic synthesis and a vast variety of reducing agents have been introduced for this achievement.¹ Among the powerful and mild reducing agents which have been developed for the reduction of functional groups, LiAlH₄ and NaBH₄ are the most commonly used reagents in synthetic organic laboratories. Lithium aluminum hydride is an exceedingly powerful reducing agent capable of reducing practically all-organic functional groups. Consequently, it is quite difficult to apply this reagent for the selective reduction of multifunctional molecules. On the other hand, sodium borohydride is a relatively mild reducing agent, primarily used for the reduction of reactive functional groups in protic solvents. However, modifying the reducing power of NaBH₄, has been realized by: (i) substitution of the hydride(s) with other groups which may exert marked steric and electronic influences upon the reactivity of the substituted complex ion,² (ii) variation in the alkali metal cation and metal cation in the complex hydride,³ (iii) concurrent cation and hydride exchange,⁴ (iv) use of ligands to alter behavior of the metal hydrides,⁵ (v) combination of borohydrides with metal, metal salts, Lewis acids, mixed solvent systems or some other agents,^{6,7} (vi) changing of the cation to quaternary and phosphonium borohydrides,⁸ and finally (vii) use of polymers and solid beds for supporting the hydride species.⁹

On the other hand, the economical demands and the existing state of environment have generated a need for paradigm shift to perform chemical reactions by using ecologically safe reagents or media. Organic reactions, carried out in dry media, have recently received careful attention with advantages (a simply work-up procedure, energy saving, avoidance of solvent waste, dangers and toxicity) over the solution reactions.¹⁰

In continuation of our earlier works on the application of ball-milling^{11, 12} in solvent-free organic synthesis, we now report a facile, environmentally friendly and clean reduction of carbonyl compounds to the corresponding alcohols with quantitative yield.

Result and Discussion

Recently, sodium borohydride has been used for the reduction of aldehydes and ketones to their corresponding alcohols in protic solvents, especially ethanol, isopropyl alcohol or CH_3CN in the presence of MoCl_5 ¹³. On the other hand, the solid state reduction of carbonyl compounds can be achieved by NaBH_4 in the presence or absence of mineral solid supports, for example wet SiO_2 under normal condition or microwave irradiation with some facilities and limitations¹⁴. Therefore, we decided to study ball milling as a new method to carry out the reduction of carbonyl compounds by NaBH_4 under solvent-free conditions (Scheme 1).



Scheme 1. Solvent-free reduction of carbonyl compound

The reduction of 1 mmol of *p*-chloro benzaldehyde as a model compound by 1 mmol of NaBH_4 under solvent-free condition took place with 100% conversion after 10 min at room temperature. Further experiments with 0.5 mmol and 0.25 mmol of NaBH_4 have also converted the *p*-chloro benzaldehyde to its alcohol, quantitatively. This amount of NaBH_4 was taken for the reduction of various structurally different aliphatic and aromatic aldehydes. The reactions were carried out quantitatively at room temperature. All reactions were completed in less than 15 min affording the corresponding primary alcohols in 100% yield (**Table 1**).

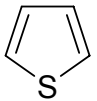
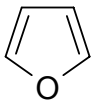
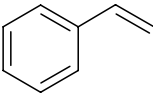
The method is superior, as it works quantitatively, with no waste, or any need of further purification. Mps and spectral data of the reaction products correlate well with the literature values.

As it is shown in Table 1, Ketones (**entry 20-25**) reacts quantitatively at room temperature to their corresponding secondary alcohols in less than 1 h and excellent yields. However, some ketones (**entry 21, 23**) need generally higher temperatures. *p*-Nitro acetophenone (**entry 22**) and benzil (**entry 24**) which were partially reacted in the similar methods¹³, react quantitatively to their corresponding alcohols by ball milling. However, some other ketones like anthraquinone (**entry 26**), xanthone (**entry 30**), benzophenone (**entry 27**) or *p*-fluorobenzophenone (**entry 28**) remain unreacted, even at elevated temperatures.

Conclusion

Ball-milling is an effective and simple method for the reduction of carbonyl compounds. The procedure includes milling a mixture of NaBH_4 and the carbonyl compound in the absence of any organic solvent. The reaction is promoted in 10-20 minutes at room temperature for the aldehydes, although ketones require higher temperatures.

Table 1. Reduction of aldehydes and ketones (**1**) by NaBH₄ (**2**) under solvent-free conditions giving alcohols (**3**)

| Entry | R1 | R2 | Mp (⁰ C) | Temp. (⁰ C) | Time (min.) | Yield (%) |
|-------|----------|---|----------------------|-------------------------|-------------|-----------|
| 1 | H | <i>p</i> -ClPh | 68-70 (67-70) | r.t | 10 | 100 |
| 2 | H | <i>m</i> -NO ₂ Ph | 28-30 (30) | r.t | 10 | 100 |
| 3 | H | <i>o</i> -NO ₂ Ph | 70-72 (72) | r.t | 10 | 100 |
| 4 | H | <i>p</i> -BrPh | 76-78 (77-78) | r.t | 10 | 100 |
| 5 | H | <i>p</i> -CNPh | 42-44 (42-44) | r.t | 15 | 100 |
| 6 | H |  | Oil | r.t | 15 | 100 |
| 7 | H | <i>p</i> -N(Me) ₂ Ph | Oil | r.t | 20 | 100 |
| 8 | H | <i>p</i> -MePh | 50-52 (50-52) | r.t | 15 | 100 |
| 9 | H | <i>p</i> -OMePh | oil | r.t | 15 | 100 |
| 10 | H |  | oil | r.t | 15 | 100 |
| 11 | H | CH ₃ CH=CH | oil | r.t | 15 | 100 |
| 12 | H | <i>p</i> -OHPh | 116-118 (115-118) | r.t | 15 | 100 |
| 13 | H | <i>o</i> -OMePh | oil | r.t | 15 | 100 |
| 14 | H | <i>p</i> -NO ₂ Ph | 94-96 (94) | r.t | 10 | 100 |
| 15 | H | CH ₃ (CH ₂) ₆ | Oil | r.t | 15 | 100 |
| 16 | H | <i>o</i> -OHPh | 71-73 (73) | r.t | 15 | 100 |
| 17 | H | Ph | Oil | r.t | 10 | 100 |
| 18 | H |  | 33-34 (30-31) | r.t | 15 | 100 |
| 19 | Vanillin | | 102-104 | r.t | 15 | 100 |
| 20 | Me | CH ₃ (CH ₂) ₄ | Oil | r.t | 30 | 100 |
| 21 | Me | <i>p</i> -OHPh | 134-136 (136) | 60 | 60 | 100 |
| 22 | Me | <i>p</i> -NO ₂ Ph | oil | r.t | 30 | 100 |
| 23 | Me | <i>m</i> -OHPh | 110-112 | 60 | 30 | 100 |

Experimental section

The ball-mill was a Retsch MM 200 swing mill with a 10 mL stainless steel double-walled beaker with fittings for circulating coolants. Two stainless steel balls with 12 mm diameter were used. Ball-milling was performed at 20-25 Hz frequency usually at room

temperature (without circulating liquid the temperature did not rise above 30°C). Water or methanol of the appropriate temperature was circulated for heating or cooling. All the products were identified by comparison of their spectral data and/or melting point with those reported in literatures.^{15, 16}

General procedure for reduction of aldehydes and ketones

In a clean and dry ball-mill vessel with 2 stainless steel balls, 1 mmol of an aldehyde or a ketone and 0.25 mmol NaBH₄ were added. After 10 min milling, the progress of the reaction was monitored by TLC. The milling cycle was repeated, if necessary, until the reaction was completed. Water was then added to the reaction mixture and the alcohol was extracted with CH₂Cl₂.

Acknowledgements

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